

REMARKS

Claims 23, 25, 26, 29, 31, and 37-39 are pending in this application. By this Amendment, claims 23 and 31 are amended, claims 32-36 are canceled, and a Declaration Under 37 C.F.R. §1.132 ("Declaration") is presented. The Declaration describes the state of the art and presents evidence in response to the alleged deficiencies (*see* October 24, 2009 Office Action) of Applicants' previous response and Declaration Under 37 C.F.R. §1.132 submitted on July 22, 2008. Support for the amendments to the claims may be found, for example, in the specification at page 7, lines 1-2 and in canceled claim 32. No new matter is added.

Applicants also thank the Examiner for the withdrawal of the objection to claim 31, the rejection of claims 23 and 31 for lack of enablement, and the rejection of claims 25, 26, and 29 as obvious over the combination of Sakamoto, WO 97/38313, and Varilek.

In view of the foregoing amendments, following remarks, attached Declaration, and the July 22, 2009 Response and Declaration, Applicants respectfully request reconsideration and allowance of the claims.

I. Rejections Under 35 U.S.C. §103

The Office Action rejects claims 23, 25, 26, 31, 32, 37-39 under 35 U.S.C. §103(a) as obvious over Sakamoto in view of Bigazzi and Pica. The Office Action rejects claims 23 and 29 under 35 U.S.C. §103(a) as obvious over Sakamoto in view of Bigazzi and Pica and further in view of Varilek. The Office Action rejects claims 23 and 33-36 under 35 U.S.C. §103(a) as obvious over Sakamoto in view of Bigazzi and Pica and further in view of U.S. Patent Application Publication No. 2003/0104364 to Billing-Medel et al. ("Billing-Medel"). Because these rejections are related, they are addressed together. By this Amendment, claims 32-36 are canceled, rendering their rejection moot. As to the remaining claims, Applicants respectfully traverse the rejections.

Without conceding the propriety of the rejections, claim 23 is amended to recite: "wherein the biological sample is blood." The method of amended claim 23 would not have been rendered obvious by the applied combinations for at least the following reasons.

A. The Deficiencies of Sakamoto, Pica and Bigazzi

The Office Action acknowledges that Sakamoto does not teach or suggest determining the presence of NGF in blood. However, the Office Action asserts that because Pica and Bigazzi allegedly disclose the presence of NGF in the serum of cancer patients, it would have been obvious to test for NGF in serum to diagnose breast cancer. Applicants respectfully assert that in light of the newly presented evidence, amendments, and arguments, there is no prima facie case of obviousness, and the evidence of record rebuts even the allegation of a prima facie case of obviousness. Therefore, the combination of Sakamoto, Pica, and Bigazzi is insufficient to establish obviousness for at least the following reasons.

1. Deficiencies of Sakamoto

Sakamoto is directed to the relationship between breast cancer cells, NGF, the high-affinity NGF receptor (TrkA), and the low affinity neurotrophin receptor (p75NGFR). Indeed, the receptor based study of Sakamoto is tissue focused, particularly because the receptors are found on the breast cancer cells. Even more, Sakamoto discloses that "NGF expression is a poor prognostic factor and that p75NGFR expression is a noteworthy factor in the prognosis of IDBC patients." *See* Sakamoto at page 976. Thus, Sakamoto teaches away from using NGF at all as a prognostic tool. Rather, it focuses on cell receptors, not NGF expression. In contrast, the method of claim 23 focuses specifically on NGF in blood. As a result of these contrasting teachings, it would not have been obvious, or predictable, for one of ordinary skill in the art to use NGF expression as a diagnostic tool, let alone use NGF expression in the blood as a diagnostic tool.

What's more, the Office Action notes when discussing Sakamoto that Applicants have "only demonstrated an increase in NGF in the serum," not in "bone marrow, milk, cerebrospinal fluid or urine." *See* Office Action at page 5. However, by this Amendment, the biological sample does not include bone marrow, milk, cerebrospinal fluid or urine, and as a result, the Office Action's comment is moot.

2. Deficiencies of Pica and Bigazzi

In response to the July Response and Declaration, the Office Action states that "Applicants have not disclosed sufficient reasons as to why one skilled in the art would not expect the secreted protein, NGF, to be found in the serum in patients with tumors overexpressing NGF, in light of the findings of Bigazzi et al and Pica et al." *See* Office Action at page 6. Submitted herewith is a further Declaration by Genevieve Chocquet-Kastylevsky, one of the inventors, directly addressing these alleged deficiencies.

a) Sakamoto and Pica

Pica relates to a cancer that is significantly different from breast cancer. Breast cancers (mammary carcinomas) are "pure" epithelial, hormone-dependent carcinomas that are exceptionally muco-secreting. *See* Declaration at paragraph 18. On the other hand, Kaposi sarcoma, disclosed in Pica, is a malignant mesenchymatous tumor made of a proliferation of spindle-shaped cells and neoplastic endothelial cells. *See id.* In particular, Kaposi sarcoma tumors are linked to AIDS and are induced by an oncogenic virus, HHV-8. *See id.* Simply put, the histological and epidemiological differences between breast cancer and Kaposi sarcoma are substantial. *See id.*

One of ordinary skill in the art would have recognized the substantial differences between breast cancer and Kaposi sarcoma and, thus, recognized that the alleged teachings of Pica in combination with Sakamoto would not create a predictable expectation of success in the unpredictable field of breast cancer diagnosis. *See* MPEP §2143.01(III) ("The mere fact

that references can be combined or modified does not render the resultant combination obvious unless the results would have been predictable to one of ordinary skill in the art.").

What's more, given the state of the art at the time of the invention, the presence of NGF in the serum of Kaposi sarcoma patients would not have been recognized even as a useful diagnostic tool for diagnosis of Kaposi sarcoma. As noted above, Kaposi sarcoma tumors are linked to AIDS and are induced by an oncogenic virus, HHV-8. Submitted herewith is a May 2000 paper by Francesca Pica et al. (the same primary author as in the applied Pica reference), which discloses that levels of NGF are found in serum from individuals with HHV-8, regardless of whether they also have Kaposi sarcoma tumors. Pica et al., *Autocrine nerve growth factor is essential for cell survival and viral maturation in HHV-8-infected primary effusion lymphoma cells*, 95 Blood 2905 (May 1, 2000). With these teachings in mind, one of ordinary skill in the art at the time of the present invention would not have understood that NGF in serum is predictably a result of Kaposi sarcoma. Rather, in view of these teachings, one of skill in the art would have at most understood that HHV-8, an oncogenic virus that can cause Kaposi sarcoma, may be responsible for increased NGF levels in serum. Thus, one of ordinary skill in the art would have understood that an individual with HHV-8 may predictably have increased levels of NGF. However, one of ordinary skill in the art at the time of the present invention would not have understood that the cancer tissue of Pica, rather than HHV-8, was responsible for the increased NGF levels reported in Pica.

Thus, Pica would not have made it obvious or predictable that the NGF of Sakamoto could have been usefully detected in blood as a marker for breast cancer according to the method of claim 23.

b) Sakamoto, Pica, and Bigazzi

Bigazzi also relates to a cancer that is substantially different from breast cancer. Medullary thyroid carcinomas, disclosed in Bigazzi, are classified among neuroendocrine

tumors and mostly produce calcitonin. *See* Declaration at paragraph 18. These cancers are classified in a special group of carcinomas: the group of the neuroendocrine carcinomas that also includes neuroendocrine tumors present in other organs such as in the lungs. *See id.* As with Kaposi sarcoma and breast cancer, the histological and epidemiological differences between breast cancer and medullary carcinoma are substantial. *See id.* For example, the thyroid, a member of the endocrine system, secretes its produced proteins directly into the blood. In contrast, mammary tissue is epithelial tissue that secretes milk. One of ordinary skill in the art would have recognized the substantial differences between breast cancer and medullary carcinoma and, thus, recognized that the alleged teachings of Bigazzi in combination with Sakamoto would not create a predictable expectation of success in breast cancer diagnosis. Further, it would not have been obvious that proteins secreted by breast cancer tissue would be suitably detectable in blood, as required by the subject claim.

In addition, Bigazzi discloses what would have been considered a unique outlying case study relating to medullary carcinoma. As such, one of ordinary skill in the art would not have reasonably applied the alleged teachings of Bigazzi to an unrelated cancer diagnostic method. Specifically, Bigazzi discloses the presence of a factor, which appears to be unconfirmed as NGF, in a medullary carcinoma patient. Even more, Bigazzi discloses high levels of this factor in one of the patient's sons, who was apparently clinically normal. Thus, one of ordinary skill in the art would have readily identified the unusual and unexplained nature of the clinical study of Bigazzi, recognized the substantial differences between breast cancer and medullary carcinoma, and concluded that application of the teachings of Bigazzi, alone or with Pica, to Sakamoto would not result in a predictable expectation of success in breast cancer diagnosis methods according to the subject claim required to establish a *prima facie* case of obviousness.

B. Other Neurotrophins Expressed but not found in Serum

In addition to the deficiencies of Pica and Bigazzi, Applicants also present experimental evidence showing that even were the teachings of Pica and Bigazzi to be considered, it would not have been predictable to detect NGF in serum. The Office Action asserts that because Pica and Bigazzi allegedly teach detecting NGF in serum for medullary carcinoma and Kaposi sarcoma, it would have been obvious to test blood for NGF to diagnose breast cancer. *See* Office Action at page 4. Specifically, the Office Action states that the previous data directed to a protein secreted by colorectal cancer tissue that is not found in blood is not sufficiently convincing to overcome the rejections. *See* Office Action at page 5. Applicants in response present even more directly applicable evidence with identified and known proteins from breast cancer tissue.

NGF is the prototypic member of the neurotrophin family of growth factors. The Declaration demonstrates that other known neurotrophins are expressed by breast cancer cells but not found in the serum of breast cancer patients. Specifically, NT4/5 and Brain-derived neurotrophic factor (BDNF) are expressed in breast cancer cells but are not present in the serum of breast cancer patients. Thus, the presence of NGF in serum would not have been predictable because other, closely related, neurotrophins expressed by breast cancer cells are not present in serum. *See* Declaration at paragraphs 7-12.

C. Conclusion

It would not have been obvious to combine Sakamoto, Pica, and Bigazzi, or to achieve the claimed method in view of those references, to achieve the method of claim 23. Independent claim 31 also would not have been rendered obvious by the combination of Sakamoto, Bigazzi, and Pica for at least the reasons presented above with respect to claim 23. Varilek and Billing-Medel do not, nor are they asserted to, cure the above-described deficiencies.

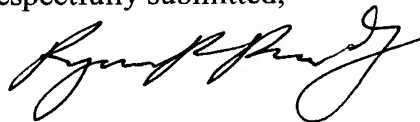
Claims 23 and 31 would not have been rendered obvious by the applied references. Claims 25, 26, 29, 32-39 variously depend from claim 23 and, thus, also would not have been rendered obvious by the applied references. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

I. Conclusion

In view of the foregoing, it is respectfully submitted that this application is in condition for allowance. Favorable reconsideration and prompt allowance of the application are earnestly solicited.

Should the Examiner believe that anything further would be desirable in order to place this application in even better condition for allowance, the Examiner is invited to contact the undersigned at the telephone number set forth below.

Respectfully submitted,



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Attachments:

Pica et al., *Autocrine nerve growth factor is essential for cell survival and viral maturation in HHV-8-infected primary effusion lymphoma cells*, 95 Blood 2905 (May 1, 2000) (Submitted in the simultaneously filed IDS).
Declaration Under 37 C.F.R. §1.132.
Information Disclosure Statement

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